Encephalitis Caused by Herpes Simplex Virus Type 2, Successfully Treated with Acyclovir: Case Report

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Abstract

Herpes simplex encephalitis (HSE) is one of the most devastating infections of central nervous system (CNS), associated with high mortality and severe neurologic sequelae among survivors. Detection of HSV-DNA in cerebrospinal fluid (CSF) by PCR is the “gold standard” for confirmation of diagnosis.

Clinical Case: thirteen-year-old girl became sick with sub-febrile temperature, catarrhal symptoms and hearing loss followed by behavioral changes. On admission, she was inadequate and excited. Neurologic examination found no signs of meningeal irritation. Laboratory investigations revealed normal blood and CSF parameters; positive HSV-2-DNA in CSF by PCR; normal cranial CT-scan. Electroencephalography registered signs of ictal episodes. Intensive treatment including acyclovir was performed. After 30-days-hospital period with persistent agitation, the patient was discharged with unchanged psychotic status. One-month-follow-up control examination did not show improvement, but one month later all psychotic symptoms suddenly disappeared.

Conclusion: Awareness for HSE and early initiation of acyclovir therapy are crucial for favorable outcome.

Keywords: Herpes simplex virus type 2; Herpes simplex encephalitis; PCR of CSF; Acyclovir

Introduction

The incidence of infections caused by herpes simplex viruses (HSV) has increased worldwide over the last several decades. Those neurotropic DNA-viruses are responsible for a wide variety of disease states and a serious neurological morbidity and mortality. There are two existing types: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), with 50% genetic homology between them but with different epidemiology and clinical manifestation [1]. HSV-1 is usually transmitted by the saliva or through direct contact with infectious secretions and causes skin lesions (called cold sores or fever blisters). HSV-2 causes genital lesions and is principally acquired sexually or spreads during delivery from an infected mother to a newborn [2]. Regardless of the available antiviral therapy, the HSE remains as one of the most unpredictable and devastating infections of the CNS that can cause focal or general signs of cerebral damage and reaches up to 70% mortality in non-treated. Only a minority of the survived individuals (approximately 9.1%) return to a fully normal brain function [2-4]. HSE is the most common sporadic fatal encephalitis in USA and Western countries [2,3,6,7]. The HSE can occur at any time of the year in patients of all ages and affects both genders equally [2,3,5]. After neonatal period HSV-1 is implicated in most of the causes of HSE, however HSV-2 can also be rarely involved in 1% to 6% of all the cases [1,3,8,9]. HSV-2 is more often associated with monophasic or recurrent aseptic meningitis in adults (previously classified as “Mollaret’s meningitis”) and also myelitis or radiculitis [1,4,8]. Approximately one third of all the cases with HSE are children and adolescents (between 6 months and 20 years) [2,3,8]. Therefore, it is of a major importance to consider the diagnosis of HSE as soon as possible.

The exact pathogenesis of the HSE is still unclear. The primary infection occurs when the virus comes in contact with mucosal surface or wounded skin. The virus starts to replicate at the site of infection and the de-enveloped capsid is transported by a retrograde way to peripheral sensory ganglia – usually the trigeminal for HSV-1 or the dorsal sacral ones for HSV-2. There, after another round of replication, the interaction between the host immune response and the viral factors can lead to a severe infection, but more often the virus remains latent and persists in the human for a lifetime. It is suggested that brain infection occurs by a direct viral transmission from a peripheral...
site to the brain via the trigeminal or olfactory nerve [1,2,7]. The HSV-associated neurological disorders can be a result from a primary infection or reactivation of a latent virus. Simultaneous presence of a skin lesion along with infection of CNS caused by herpes simplex virus is rare. Recently performed studies indicate that approximately one-third of the cases of HSE are consequences of primary infection. Besides, in children and young adults HSE appears most often during primary infection [2,7]. HSV-1 usually affects temporal or orbitofrontal lobes, whereas the HSV-2 affects those areas less often and may demonstrate a predilection for the brainstem [1,2,5,9]. Adjacent limbic areas can be also affected [2,7]. The mechanism of cellular damage includes both direct virus-mediated and indirect immune-mediated processes. The typical pathologic changes in the infected cells are ballooning and an appearance of chromat in within the nuclei, followed by a degeneration of the cellular nuclei. The separate cells lose plasma membranes and form giant cells. The result is acute focal, necrotizing encephalitis with inflammation, swelling, congestion and/or hemorrhage of the brain tissue [2].

There are no pathognomonic clinical features distinguishing HSE from other neurological diseases with similar presentation. This not allows empirical diagnosis of the disease based only on the clinical presentation. According to most of the authors, HSE is suspected in a patient with a low-grade fever, changes in personality and focal neurologic signs [2,3,10,11]. Frequently, especially in children, the clinical presentation of HSE can be atypical or subacute with lack of fever in the early days of the disease, manifestations of meningeal syndrome or behavioral changes only [3,12]. Although the mortality of acyclovir-treated patients with HSE decreases, the morbidity remains high with poor long-term neurologic outcomes. The consequences among the survivors depend on their age, pre-morbid immunity and neurological status at the time of diagnosis. Some neurologic changes and complications may appear several years after the disease. Therefore, a long term examinations of the survived patients must be performed to evaluate the real outcomes of HSE.

Since HSE are not common and provoke diagnostic and therapeutic difficulties; we aimed to present the first for our Clinic of Infectious Diseases case of confirmed and survived without sequel HSV-2 encephalitis.

**Case Presentation**

On 15th August 2015, a thirteen-year-old female patient fell ill with sub-febrile body temperature up to 37.5º C, catarrhal symptoms of the upper respiratory tract and hearing loss. She was examined by oto-rhino-laryngologist which prescribed a symptomatic treatment. In the next day, the parents observed behavioral changes in the child expressed by panic attacks, shivering, slurred speech, and intolerance to light and sound. She was disoriented, at some moments inadequate and she had a single generalized seizure with convulsions, lock jaw and muscle stiffness, cyanosis of the lips, and staring. The girl had admitted in Ward of Infectious Diseases at the regional hospital on 17th August 2015. Despite the performed treatment with cefazidime, amikacin, anticonvulsants, dexamethazone, and mannitol, the general condition of the patient was worsening with a persisting psychosis. Therefore, on 19h August, 2015 she was consulted with specialist of Infectious diseases from University Hospital–Pleven. During the examination, the girl was fallen in severe psychomotor agitation with aggressive behavior. This demanded involvement of a reanimation team and intravenous sedation. Afterwards, the girl was transported and admitted in Clinic of Infectious Diseases at University Hospital–Pleven with diagnosis viral encephalitis with unknown etiology. A written Informed Consent signed by parents was obtained.

About pre-morbid and epidemiological history, parents reported that the girl had been suffering from an unspecified rhinitis for many years. Additional information for recent sexual intercourse with person with genital HSV infection was obtained.

On admission in University Hospital – Pleven, the patient was in a severe condition, inadequate, with psychomotor agitation and sub-febrile body temperature (37.6 ºC). The skin was without rash and other lesions. Physical examination revealed increased heart rate (120 beats per minute) and hepato-megaly. No pulmonary auscultation findings were registered. Neurologic examination had not revealed any signs of meningal irritation. The patellar and Achilles reflexes were symmetrical but hyperactive. No pathological reflexes were found. Cranial nerves were intact. Pupils were equal with a good reaction to light.

Laboratory investigations on admission revealed leukocytosis with neutrophilia, thrombocytosis and slightly elevated C-reactive protein. Urine sample revealed proteinuria, 5-10 leucocytes and 5-10 erythrocytes in the sediment. Liver functional tests, serum protein concentrations, nitrogen parameters, blood glucose level and electrolytes were in reference ranges (Table 1).

Lumbar puncture was performed twice – on the day of admission and ten days later. The first CSF investigation revealed protein level of 0.15 g/L, leucocytes 10/mm³ and glucose 4.5 mmol/L. The second CSF investigation (on 29th August, 2015) revealed protein level of 0.35 g/L, leucocytes 3/mm³ and glucose 3.57 mmol/l. A CSF-sample was sent to University Hospital – Pleven for Enteroviruses DNA, negative for HSV-1 DNA and positive for HSV-2 DNA.

| Table 1: Laboratory investigations of the reported case after admission. |
|-----------------------|--------|--------|--------|--------|
| Laboratory parameters | 1st day | 6th day | 16th day | 27th day |
| Hemoglobin (g/L)       | 116    | 127    | 124    | 123    |
| Erythrocytes (cells x 10¹²/L) | 3.91    | 4.35    | 4.22    | 4.15    |
| Hematocrit            | 0.33   | 0.37   | 0.38   | 0.36    |
| MCV                   | 85     | 87     | 87     | 86      |
| Leucocytes (cells x 10⁹/L) | 16.1    | 18.3    | 11.4   | 8.3     |
| Granulocytes (%)       | 90     | 89     | 62     | 56      |
| Lymphocytes (%)        | 8      | 8      | 30     | 35      |
| Monocytes (%)          | 2      | 3      | 7      | 8       |
| Platelets (cells x 10⁹/L) | 472    | 451    | 368    | 329     |
| Total protein (g/L)    | 64     | 69     | -      | 64-83   |
| Albumins (g/L)         | 43     | 51     | -      | 35-50   |
| Glucose (mmol/L)       | 5.28   | 5.44   | 4.53   | 3.89-6.11 |
| C-reactive protein (mg/L) | 7.31    | 1.2    | -      | 14.22   | 0-5.00   |

Immuno-phenotypization of lymphocytes-subsets, performed by FACSort flow-cytometer, revealed lymphopenia (4.86%; N 36-43%), normal total T-lymphocytes count (CD3+) (69.14%; N 66-76%); increased T-helpers/cytotoxic T-cells ratio (CD4+/CD8+) (1.98; N 1.1-1.4) with T-helpers on the upper level of normal range (CD4+) (41.22%; N 33-41%) and decreased cytotoxic T-cells (CD8+) (20.79%; N 27-35%); B-lymphocytes on the upper level of normal range (CD19+) (22.22%; N 12-22%) decreased NK-cells (CD3+/CD56+16+) (3.12%; N 9-16%). The interpretation of these results concluded that disorders of cellular immunity had presented. Cranial CT scan was considered as normal.

The electroencephalogram (EEG) (on 15th September, 2015) revealed a focal activity in the right parietal-temporal-occipital area.
with a significant secondary bilateral spontaneous synchronization. Long sections of hyper-synchronous activity were observed widely on the right side. Background activity was with dominant theta-rhythms in the slow theta-range and with an episodic display of alpha-rhythm with a bilateral frontal peak. The conclusion was that there are electroclinical findings of ictal psychiatric episodes (Figure 1).

The patient was consulted and discussed with neurologist, psychiatrist and oto-rhinolaryngologist. The treatment was performed by intravenous administrations of dexamethazone (initial dose 24 mg/24 h, 27 days), mannitol 10%, Human-Albumin 20% 100 ml (5 times), immunovenin 50 ml (7 times), glucose and saline solutions, ceftriaxone (2g twice daily intravenously, 14 days), sulfampicillin (1.5 g trice daily intravenously, 13 days) and fluconazole intravenously (7 days), vitamins. On the 7th day of hospitalization, a HSV etiology of the disease was considered and acyclovir was started with a daily dose of 30 mg/kg/24 h intravenously for 20 days. Severe excitation was treated with midazolam intravenously (15mg/50 ml daily, 26 days). Anticonvulsive therapy was performed orally by oxcarbazepine, phenytoin and depakine. Despite the treatment, the patient was in severe condition during the whole hospital period with a persistent, slowly to overcome psychomotor agitation and aggressive behavior. She was contactable, but inadequate; afebrile and without dyspeptic symptoms. There were changing stages of logorrhea, perseverations, and chaotic speech with single short episodes of meaningful and adequate phrases. Switching phases of continuous insomnia interchanged with short ones of sleep. The girl was anorexic, spitting out the foods and medications. She was discharged on the 30th day after admission with normal vital functions and no signs of meningeval irritation, but with unchanged psychotic status. Instructions for continuous treatment with anticonvulsants were given along with a neurologist. Control investigations were performed on 15th and 30th day after discharge and revealed no significant behavioral changes. Two months after hospital discharge, during traveling to home after control examination, the girl suddenly realized a contact with her parents, became completely adequate and in clear consciousness, but with retrograde amnesia for full time since the clinical onset. Until the present moment, she is in good general condition, without psychotic episodes and no behavioral changes. She continues to accept part of antiepileptic medications.

**Discussion**

Independent on the fact that the incidence of infections caused by HSV has increased worldwide, incidence of HSE varies in the general population from 1 to 4 cases per 1 million individuals [2,3,6,7]. Approximately one third of all cases with HSE are children and adolescents (between 6 months and 20 years) [2,3,8]. After neonatal period HSV-1 is implicated in most of the causes of HSE, however HSV-2 can also be rarely involved in 1% to 6% of all cases [1,3,8,13]. HSV-2 is more often associated with monophonic or recurrent aseptic meningitis in adults (previously classified as "Mollaret’s meningitis") and also myelitis or radiculitis [1,4,8]. In difference of this comprehension, here reported case had typical clinical presentation as encephalitis.

As it was mentioned above, the lack of pathognomonic clinical features distinguishing HSE from other neurological diseases with similar presentation provokes diagnostic difficulties in the early phase of disease. According to most of the authors, HSE is suspected in a patient with a low-grade fever, changes in personality and focal neurologic signs [2,3,11,12]. Patients with HSE usually have flu-like prodromal period with fever, malaise, headache, nausea and additional symptoms such as drowsiness, confusion and disorientation [5,12]. In accordance with these observations, the clinical onset in our patient also began with sub-febrile temperature up to 37.5°C and cattarrhal symptoms of the upper respiratory tract.

After the appearance of the initial symptoms, the affected patients may develop focal or generalized seizures, speech abnormalities, memory loss, behavioral changes as hyperactivity or psychotic episodes and other psychiatric symptoms [2,7,10,11]. The mentioned clinical signs were too similar to these observed in our case.

Clinical findings, similar to the associated with meningitis such as stiff neck, Kerning’ and Brudzinski’ signs, altered tendon reflexes and positive reflex of Babinski, headache, vomiting and photophobia could be present [10]. Loss of consciousness, hallucinations and hemiparesis are uncommon [5,10]. In here presented case, neurologic examination revealed only hyperactive tendon reflexes, without pathological reflexes. This confirms the fact that frequently, especially in children, the clinical presentation of HSE can be atypical or subacute with lack of fever in the early days of the disease, manifestation of meningeal syndrome or behavioral changes only [3,12]. If more of specific clinical features are initially missing, they might appear during the following days. This requires precise clinical and neurologic examinations to be daily performed [3].

There are many reports that describe acute opercular syndrome as one of the possible clinical presentations of HSE. Opercular syndrome is a disorder and damage of the facio-linguo-glosso-pharyngeal muscles which leads to jaw stiffness, dysarthria and dysphagia [3,14]. We consider that observed since clinical onset slurred speech, lock jaw, muscle stiffness, cyanosis of the lips, and stares coincide with here mentioned literature data.

The diagnosis of HSE is based on the complex of detailed patient history, evaluation of the clinical features, neurodiagnostic tests and laboratory techniques. The results of routine laboratory tests are usually within normal ranges as it had observed in our patient. The CSF biochemical findings are non-specific and similar to the results typical for the most viral encephalitis – the number of leukocytes.
with prevalence of lymphocytes and the protein concentration both become elevated as the disease progresses [2,3,7]. According to different sources, CSF might be even normal on first evaluation in 5-10% of cases [2,3,15]. This consideration coincides with our observations – both CSF samples revealed normal parameters.

The etiology of HSE can be confirmed by a variety of techniques – brain biopsy, serological analysis of HSV antibodies and detection of HSV-DNA in CSF using polymerase chain reaction (PCR). Brain biopsy is rarely used in present practice and has been essentially replaced by PCR, which nowadays is considered to be the "gold standard" for confirmation of diagnosis of HSE [2,3,9,12]. The viral load in the CSF (viral DNA copies/mL) correlates with clinical outcome and can be used to evaluate the prognosis of the disease [16]. PCR results need to be interpreted along with the patient’s clinical presentation and the timing of taking sample of CSF. According to the different authors the sensitivity and specificity of the method are both above 90% for adults, and around 70% for children [1,2,3,15]. False negative results can occur mostly in children, as well as if the CSF is taken too early (first 24 to 48 h) or too late (after 10 to 14 days) and if acyclovir is administered too early [4,12,15]. According to these considerations, we obtained and sent CSF sample for PCR on 12th day after clinical onset (9th day after initiation of treatment with acyclovir). Viral CSF cultures are often negative and should not be relied on to confirm the diagnosis [1,5]. Measurement of the CSF intrathecal antibodies is usually used for retrospective diagnosis and is not recommended for acute diagnosis [4,7,15]. Serologic analysis is useful to define whether HSE is a result of primary or reactivated HSV infection [4,12]. Due to this reason, we did not performed serologic investigation of CSF.

Neurodiagnostic tests such as EEG and cerebral imaging techniques are beneficial in diagnosing and should be considered in each presumptive case for HSE. The sensitivity of EEG is approximately 84%, but the specificity is only 32.5% [2,5]. There is no specific EEG pattern in patients with HSE. The focal changes of the EEG described in literature are characterized by spike and slow-wave activity and periodic lateralized epileptic form discharges, which arise from the temporal lobe [2,3,7,8,17]. EEG performed in our patient revealed a focal activity in the right parietal-temporal-occipital area with an increased membrane potential and rhythmic bursts of 2-3 Hz activity. The EEG findings were consistent with the clinical presentation of the patient. According to some authors, the neurological sequels are as follows: approximately 38% of cases are with no or mild deficits, 9% are with moderate deficits, 53% are with severe deficits or died [2,5]. The most frequent neurological sequel include mental retardation and memory impairment (69%), behavioral impairment (45%), dysphasia (41%) and focal motor deficits and/or epilepsy (25%) [3]. Relapses are reported to occur in 5-26% of the patients, more frequently in children than adults, and most relapses are occurring in the first three months after the treatment course [3,5]. Some neurological changes and complications may appear several years after the disease. Therefore, a long term examinations of the survived patients must be performed to evaluate the real outcomes of HSE. Independent on unchanged psychotic status of here presented case on discharge, she had completely recovered and during one-year-follow-up control no sequel was observed.

Conclusion

HSE is uncommon but difficult for diagnosis disease, with high
mortality risk and severe neurological sequel. Awareness for HSE and early initiation of acyclovir therapy are crucial for favorable outcome.

Consent

Written informed consent was obtained from the patient’s parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

References

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